# B. BACKGROUND AND GOALS FOR FELLOWSHIP TRAINING

## B1. DOCTORAL DISSERTATION AND RESEARCH EXPERIENCE

2016 – 2019: Research Assistant (Medical Resident), Dr. Amit J. Shah, Emory University

During my clinical training as an internal medicine resident, I had the opportunity to work with the Emory Program in Cardiovascular Outcomes Research and Epidemiology (EPICORE) group, through which I met Dr. Viola Vaccarino and Dr. Amit J. Shah. I was introduced to autonomic dysfunction as a marker of disease in both psychological processes and in cardiovascular disease. I initially studied heart rate variability (HRV) and its relationship to abnormal myocardial flow reserve. This project led to a first author manuscript, now under review, entitled “Alterations in heart rate variability are associated with abnormal myocardial perfusion”. I found that low HRV in the morning was strongly associated with reduced coronary flow reserve. This finding was novel, revealed the importance of the circadian rhythm, and introduced a more powerful HRV metric (*Dyx*). I learned how to not only prepare and clean data but perform independent statistical analyses and translate the results into scientific products (e.g. regional and national presentations, manuscript). In addition, under supervision of the mentoring team, I submitted and received approval for my own independent manuscript proposal to the Atherosclerosis Risk in Communities Study publication committee. I chose to study how psychosocial factors may lead to changes in autonomic function by measuring HRV. The study results were notable for how somatic symptoms of depression had the most robust association with low HRV, and that the changes in HRV were persistent over many years (with repeat follow-up visits as part of a prospective cohort). This project has also led to a national poster and manuscript that have been submitted. I learned and improved on scientific writing, oral presentation skills, and statistical/computational techniques. This work and mentorship shaped my ultimate research direction to study autonomic dysfunction as a risk-factor for cardiovascular disease.

2019 – Present: TL1 Postdoctoral Fellow in Epidemiology, Drs Amit J. Shah and Alvaro Alonso, Emory University

To continue my research training with the goal of becoming an independently funded physician-scientist, I applied for and received the TL1 award at Emory University in the Department of Epidemiology to obtain a Master of Science in Clinical Research (MSCR) and have protected time to pursue research in autonomic regulation of cardiac physiology. This program has provided me a solid research foundation that I will build upon as an academic clinician. With the protected research time, I conducted a pilot study to study the relationship between depression and coronary artery disease by measuring the association with HRV. This required the submission of an IRB amendment to the existing parent study, enrolling patients with ECG patches (including data extraction), signal processing using the HRV toolbox (developed at Emory), and computational techniques to analyze the resulting data. I became proficient in MATLAB and SAS, and skillful with the R programming language. I also expanded my knowledge of foundational biostatistics through the MSCR. The preliminary results show a strong association with both depression and coronary artery disease with HRV and serves as the basis for the F32 application. Through this work I have developed several research skills that I hope to expand upon by further protected research time and mentorship. This training grant will allow me to take advanced coursework in epidemiology and biostatistics to begin preparation for an NIH K Career Development Award that will be submitted at the end of my postdoctoral fellowship training.

## B2. TRAINING GOALS AND OBJECTIVES

My long-term career goal is to become an independently funded translational researcher in neurocardiology and an academic physician. I became interested in clinical research during my residency training in Internal Medicine at Emory University, where I am obtaining a MSCR through a TL1 award to facilitate this goal. My ultimate research direction focuses on elucidating the role of the autonomic nervous system in cardiovascular outcomes, which was shaped by my studies of the mind-body connection as an undergraduate student, clinical training in medicine, and postdoctoral computational and epidemiological research on the neurocardiac axis. I approach autonomic dysfunction in cardiovascular epidemiology with computational techniques to identify novel electrocardiographic risk factors that may predict outcomes and risk in psychological and cardiac disease. This post-doctoral NRSA training grant will allow for the protected time needed to develop the foundational skills to become an independently funded physician-scientist.

The F32 award will fund the two years of post-doctoral fellowship in epidemiology at the Rollins School of Public Health at Emory University. The training environment at Rollins includes the Emory Program in Cardiovascular Outcomes Research and Epidemiology (EPICORE), which is a multidisciplinary group of PhD scientists, physicians, epidemiologists, and biostatisticians that is led by my sponsor, Dr. Vaccarino, and co-sponsors, Dr. Shah and Dr. Alonso. There is strong focus on psychological factors and cardiovascular disease within this group, allowing me to collaborate with the best-suited mentors to develop into a translational researcher and clinical investigator. The multidisciplinary approach also allows novel projects, interdisciplinary dialogue, and different perspectives to be discussed during weekly meetings.

The grant will allow me to develop and enhance core skills needed on the path towards future career development awards, as outlined in **Table B1**. The three major training areas are in epidemiological and research methods, biostatistical and computational analysis, and knowledge of neural control mechanisms of cardiovascular physiology, which are essential to and build upon the research proposal. The first area of focus is on epidemiology and research methods. By taking additional courses at the Rollins School of Public Health, the grant will allow me to supplement my training and enhance my understanding of core and advanced epidemiological methodology. As both Dr. Alonso and Dr. Vaccarino have expertise in large cohort studies, including longitudinal data collection, I will learn how these studies are designed. By participating in weekly meetings, I will also learn how successful, multidisciplinary research teams operate. The sponsorship and advisory committee are also committed to my development as a clinical investigator. They will provide constructive feedback from study proposals to data interpretation and manuscript preparation.

The training proposal allows me to explore a novel approach to research autonomic dysfunction using heart rate variability (HRV), an electrocardiographic marker of sympathovagal outflow to the heart. The study also uses a prospective cohort from the Emory Cardiovascular Biobank. The combination of a large sample size with in-depth, granular data (e.g. up to 24 hours of raw ECG signal per patient) will require further development of my biostatistical and computational skills. Foundational coursework in regression modeling, statistical computing, and large-data analysis will strengthen my background in computer programming and data science. Dr. Shah, as an expert in ECG analysis, will mentor me through the analytical portion of the work. I will leverage the existing HRV toolbox, developed at Emory with Dr. Shah, which will allow me to expand my skills in time-series analysis.

The research proposal lies within the field of neurocardiology, which studies the neural or autonomic control of cardiovascular physiology, such as the effect of psychological stress on heart disease. All of my sponsors have varied expertise in this area. Dr. Vaccarino has studied depression, mental stress, and coronary vasomotor control extensively, which will help provide the background clinical knowledge needed to propose the most rigorous and meaningful research hypotheses. To best understand this applied physiology, I will pursue directed reading and application of the literature with Dr. Park, a long-standing collaborator who researches autonomic control of vascular physiology in experimental studies.

This award will allow me to prepare for a successful NIH K23 career development application. The proposed training incorporates several important aspects of clinical research. By combining my background in clinical medicine with new skills in quantitative epidemiology, psychological stress, and ECG analysis, I hope to develop a pilot study to further characterize autonomic dysfunction as a prognostic tool. This novel research will allow us to identify at-risk patients using non-invasive techniques, which will lead to potential therapies that can target autonomic dysfunction. In addition, the data collected includes raw ECG signal and creates a well-characterized cohort for future studies. This includes genetic testing and serum biomarkers, which are collected as part of the parent study protocol. Dr. Vaccarino and Dr. Alonso have received K24 awards for mentoring, as well as multiple R01 awards, and Dr. Shah has recent experience with his own K23/R03 awards, which will allow me to leverage their experience and guidance in becoming a future physician scientist.

My ultimate career goal is to become a successful clinical investigator and an academic physician. By obtaining an MSCR, devoting time to research through the TL1 award, and building a collaborative, interdisciplinary team of mentors and advisors, I have taken the first steps towards this goal. With continued dedication, perseverance, and the support obtained from this grant, I will have the capacity to succeed in a career development application and achieve my long-term goals of becoming an independently funded physician-scientist.

Table B1. Summary of Core Skills for Training and Future Mentored Research

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| **Core Skill** | **F32 Training Plan** | **Competencies** |
| Epidemiology and Research Methods | 1. Coursework: EPI 538 and EPI 545 2. Experiential Training: Research with Dr. Alonso and Dr. Vaccarino on study design 3. Mentoring meetings directed at career advancement and future K-award | 1. Understand core concepts in epidemiology 2. Understand theory needed in the design of large cohort studies 3. Gain skills needed to understand and critically interpret epidemiological studies 4. Improved manuscript and grant-writing skills 5. Research presentation skills |
| Biostatistical and Computational Techniques | 1. Coursework: BIOS 526, BIOS 534, and BIOS 731 2. Experiential Training: ECG analysis with HRV Toolbox to strengthen understanding of raw data manipulation and time-series analysis with Dr. Shah 3. Experiential Training: Statistical modeling of study variables, including linear and logistic regressions and survival analysis. | 1. Working knowledge of common statistical techniques 2. Ability to choose and perform increasingly complex statistically analyses with appropriate guidance 3. Become an informed collaborator in increasingly multidisciplinary computational methods 4. Increased understanding of MATLAB and R software programming |
| Neural Control of Cardiovascular Physiology | 1. Coursework: Directed readings with Dr. Park on autonomic physiology. 2. Weekly lab and project meetings to understand clinical implications of ANS disease with Dr. Shah, Dr. Thames, and Dr. Park. 3. Mentoring and research meetings on psychological variables effect on heart with Dr. Vaccarino | 1. Understand content and foundational literature of autonomic physiology in relationship to neurocardiology 2. Interpret psychological epidemiology concepts, in particular qualitative assessments 3. Ability to create and interpret hypotheses from foundational, mechanism-oriented knowledge |

## B3. ACTIVITIES PLANNED

If provided this NRSA award, my research training will consist of formal training, mentored research, and clinical efforts to prepare me for an early career development award as a translational researcher. This training grant will provide funding for two additional research years between July 2020 and June 2022. The detailed activities that I will undertake during these two years are provided in **Table B2**. This training grant will provide funds for advanced coursework in epidemiology and biostatistics at the Rollins School of Public Health to supplement my Master of Science in Clinical Research degree. The selected coursework will enhance my understanding in advanced epidemiologic methods (EPI 538, EPI 545) and advanced longitudinal data analysis (BIOS 526, BIOS 731, BIOS 534). This will complement and strengthen my computational training, allowing me gain in-depth knowledge and skills in study design, advanced statistical modeling, and data interpretation. Additionally, as part of my research training I will attend biweekly epidemiology grand rounds, weekly cardiovascular grand rounds, and weekly medicine grand rounds. Under the guidance of my advisor Dr. Park, an expert in this field, I will study autonomic physiology through directed reading and interpretation of clinical science through weekly lab meetings. The proposed research will be presented at two national conferences yearly. The proposed research will be completed over the two years, during which approximately two-thirds of my time will be devoted to completing this project, presenting at national meetings, and preparing manuscripts. I will attend weekly lab meetings with my primary sponsor, Dr. Vaccarino, and my co-sponsors Dr. Shah and Dr. Alonso. Additionally, I will maintain light clinical duties with inpatient hospital medicine service activities for approximately 5% of my time, which will allow me to maintain my skills/perspective in clinical translation of my research to the bedside.

Table B2. Detailed Effort for Activities Planned Under this Award

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| **Tasks** | Year 1 (% Effort) | Year 2 (% Effort) |
| Formal Training Plan |  |  |
| Formal Course Work (credit hours) |  |  |
| EPI 538 Advanced Epidemiological Methods I (2) | 5% |  |
| EPI 545 Advanced Epidemiological Methods II (4) |  | 12% |
| BIOS 526 Modern Regression Analysis (3) | 8% |  |
| BIOS 731 Advanced Statistical Computing (2) | 5% |  |
| BIOS 534 Machine Learning (3) |  | 8% |
| GAH 601 the Responsible Conduct of Research Ethics (1) | 1% | 1% |
| Didactic Lectures and Journal Clubs (frequency) |  |  |
| Epidemiology Grand Rounds (biweekly) | 1% | 1% |
| Emory Heart and Vascular Grand Rounds (weekly) | 2% | 2% |
| Emory Department of Medicine Grand Rounds (weekly) | 2% | 2% |
| K-Club Research Lectures (weekly) | 1% | 1% |
| Directed Reading in Autonomic Physiology (weekly) | 2% | 2% |
| National Conferences (two per year, three days each) |  |  |
| American Heart Association | 1% |  |
| Translational Science |  | 1% |
| American Heart Association Epidemiology | 1% |  |
| Computing in Cardiology |  | 1% |
| Total Training Effort | 29% | 31% |
| Research Plan |  |  |
| Specific Aim #1 |  |  |
| Parent study (Emory Biobank) data collection | 3% |  |
| Derive markers from ECG signals (for all aims) | 10% |  |
| Analysis of depressive symptoms with HRV | 5% | 2% |
| Explore interaction with age, and sex | 5% | 3% |
| Conference presentation and manuscript publication | 5% | 15% |
| Specific Aim #2 |  |  |
| Emory Biobank data collection | 3% |  |
| Derive exploratory coronary angiography variables | 3% |  |
| Adjust for time-dependent associations with HRV | 5% |  |
| Analysis of coronary angiography with HRV | 10% | 2% |
| Explore interaction with age and sex | 2% | 3% |
| Conference presentation and manuscript publication | 5% | 15% |
| Research Training |  |  |
| Mentor meetings | 5% | 5% |
| Exploratory analyses (ECG markers, outcomes data) |  | 4% |
| K23 grant application or equivalent | 5% | 15% |
| Total Research Effort | 66% | 64% |
| Clinical Effort |  |  |
| Inpatient General Medicine Service | 4% | 4% |
| Medical student, intern, and resident teaching | 1% | 1% |
| Total Training, Research, and Clinical Effort | 100% | 100% |